IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Bahramian et al.
Appl. No: 09/472/558
File Date: December 27, 1999
Invention: MUTING GENE ACTIVITY USING A TRANSGENIC NUCLEIC ACID
Art Unit: 1632
Examiner: Paras, Peter Jr.
Docket No.: 2498/101, formerly 2281/102

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being transmitted by facsimile to the United States Patent and Trademark Office, Alexandria, VA, 22313, to Examiner Peter Paras, Art Unit 1632, fax numbers (703) 308-4242(official copy) and (703) 746-5304 (courtesy copy), telephone number (703) 308-8340, on August 26, 2003.

Barbara J. Carter, Ph.D.

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Honorable Commissioner of Patents
Alexandria, VA

RESPONSE H

Dear Sir:

This communication is in reply to the Office communication of August 13, 2003 requiring a written summary of the substance of the Interview that occurred on August 4, 2003 between Examiner Paras, Applicant Dr. B. Bahramian, and attorneys Barbara J. Carter and Bruce D. Sunstein.

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AMENDMENTS

Amendments to 37 CFR § 1.132 Declaration, filed with Response G on August 6, 2003.

Please amend the following paragraphs in the Declaration filed on August 6, 2003:

Page 3, para. 5. Please replace paragraph 5 on page 3 with the following:

5. The first example of transgene-induced gene silencing in higher animals was provided in normal and transformed rodent cell lines, which occurred by both transcriptional and posttranscriptional mechanisms (Bahramian and Zarbl, 1999). That report, while uncoupling transcriptional and posttranscriptional mechanisms of transgene-induced muting, implicitly, by default, linked the potent and specific mRNA degradation in mammalian cells, resulting from PTGS, to the *in vivo* production of short dsRNA that act as the intermediary molecule of communication between the silenced genes in the cell nucleus and the cognate mRNA in the cytoplasm.

Pages 3-4, para. 6. Please replace para. 6 with the following:

6. Following that discovery, the mediators of sequence-specific mRNA degradation were found to be 21- and 22-nucleotide small interfering RNAs (siRNAs) generated by ribonuclease III cleavage from longer dsRNAs (Hammond et al., 2000; Zamore et al., 2000; Bernstein et al.. 2001; Elbashir et al., 2001). Thus, it was discovered what separates RNAi in higher animals from lower animals and plants was the size of effective dsRNA. While short dsRNA molecules are the actual mediators of PTGS in all animals and plants, long dsRNA only work in plants and lower animals, because in higher animals (particularly in mammals) dsRNA causes the strong "interferon

response". Furthermore, Bahramian & Zarbl's work (1999) showed that the reason for inability to show plant- and lower animal-type co-suppression in mammalian cells is certain distinctions between the silencing mechanisms in plant and lower animals versus higher animals, even though they are related by RNAi (discussed below).

INTERVIEW SUMMARY

Applicants faxed draft versions of claims 11 and 57 to the Examiner on July 25, 2003 for discussion during the Interview on August 4, 2003. Applicants also faxed an Interview Request Form on July 25, 2003, stating that they intended to discuss the addition of "screening" language in claims 11 and 57, and how it would overcome the enablement rejection, as well as deletion of the language "or having the capacity to become double-stranded" and how it would obviate the new matter rejection.

During the interview, the above points were made. The Examiner's response was that he would consider the arguments. Additional topics that were discussed during the interview include:

- arguments by Applicants that *ex vivo* data was enough for in vivo coverage. The Examiner pointed out that if muting does occur *in vivo*, there will be a phenotypic effect. Applicants agreed to discuss this in the response (already filed as Response G on August 6, 2003).

- literature citations noting the surprising lack of RNAi in mammals, considering the Applicants' discovery and paper of 1999, and how this supports Applicants' position that *in vivo* coverage is appropriate as those skilled in the art would expect *ex vivo* results to translate to *in vivo* systems. Examiner suggested the reference mentioned by Applicants be provided, and these arguments would be considered. The reference (Tuschl et al.) and arguments have been included in Response G.

- clarification of term "independent of expression" in independent claims 11 and 57. Examiner expressed the opinion that this term also encompasses transcription, so

claims need to address this point. Applicants have addressed this in the current version of claims 11 and 57 submitted with Response G.

- claims with coverage for muting nucleic acids other than DNA. Applicants argued that this technology is well-known in the field and does not need to be explicitly detailed in the specification to justify coverage, and that Examiner's position on this point is unreasonable. Examiner said he would consider Applicants' arguments.

- post-transcriptional muting and role of 3'-end gene sequences. Examiner questioned the generality of this phenomenon, and Applicants attempted to explain what is known in this area to date.

REMARKS

The amendments to the 37 CFR § 1.132 Declaration have been made for reasons of accuracy and clarity.

The interview summary, prepared to the best of Applicants' recollection, is hereby submitted. With this communication, compliance with 37 CFR § 1.133 (b) for submission of a written interview summary has been met.

For the reasons stated in Response G, filed August 6, and Supplement to Response G, filed August 19, 2003, together with the corrections to the Declaration submitted herewith, it is respectfully submitted that all pending claims are in condition for allowance. Reconsideration of the claims, consideration of the added claims, and a notice of allowance is therefore requested.

It is believed that no extension of time is needed. If any additional fees are required for the timely consideration of this application, however, please charge deposit account number 19-4972. The Examiner is requested to telephone the undersigned if any matters remain outstanding so that they may be resolved expeditiously.

Date: August 26, 2003

Respectfully submitted,

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